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Platinum Priority – Collaborative Review – Urothelial Cancer

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Diagnosis and Management of Urothelial Carcinoma In Situ of the Lower Urinary Tract: A Systematic Review

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Abstract

Context: Urothelial carcinoma in situ (CIS) has a high propensity for progression. It is usually reported within the heterogeneous context of non–muscle-invasive bladder cancer (NMIBC) but warrants special consideration.
Objective: To review the contemporary literature on the diagnosis and management of CIS.
Evidence acquisition: A systematic search using broad terms to capture the diagnosis and treatment of CIS was performed according to Preferred Reporting Items for Systematic Reviews and Meta-analysis criteria. Full-text original articles, reviews, and editorials from 1966 to 2014 in English were included. References from selected articles, relevant guidelines, and conference abstracts were searched. Abstracts were excluded.
Evidence synthesis: A total of 1887 articles were identified, of which 120 were used in this review. Most reports were retrospective and heterogeneous in caseload. There is a lack of standardised classification of CIS. Many studies consider CIS in the context of NMIBC without a clear separation of the subset with CIS. Recent prospective phase 2 and 3 studies have improved the evidence base.
Conclusions: We are beginning to understand that CIS has a spectrum of biologic potential. Bacillus Calmette-Guérin immunotherapy appears superior to other intravesical agents and may alter the natural history of CIS. New imaging modalities, agents, and treatment strategies have emerged in recent years with the aim of better identification of CIS, more bladder-preserving treatments, and prevention of surgical overtreatment.
Patient summary: Improvements in imaging techniques combined with new bladder-preserving treatments will continue to have an impact on the outcomes of bladder carcinoma in situ.

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1. Introduction

Approximately 75% of patients with urothelial cell carcinoma (UCC) of the bladder have non–muscle-invasive bladder cancer (NMIBC) [1]. Although these patients generally have an excellent prognosis despite local recurrence [2], carcinoma in situ (CIS) is a distinct form of NMIBC that warrants special consideration. CIS is a high-grade carcinoma with the potential for invasion and metastases. CIS may present in isolation or with a synchronous UCC, and it may affect the upper tracts, prostatic ducts and urethra, and penile urethra. The presence of CIS increases the risk of subsequent recurrence and progression of UCC.

Key challenges for managing CIS are in detection, prediction of behaviour, and treatment beyond bacillus Calmette-Guérin (BCG). CIS is visible with white-light cystoscopy (WLC) in about 50% of cases [3]. New methods of visualisation, including fluorescent cystoscopy and narrow-band imaging (NBI), appear to improve the detection of CIS, although their clinical impact remains to be determined [4–10]. Intravesical BCG is generally accepted as the first-line therapy for CIS. Frequent recurrences, the risk of progression, and the absence of robust second-line options make radical cystectomy (RC) the treatment of choice in case of BCG failure. High-risk NMIBC, including CIS, fails bladder preservation in approximately 50% of cases [11]. It is well established that those who progress to muscle-invasive bladder cancer on BCG have poor outcomes [12,13].

Most reports of CIS do so within the context of NMIBC. Few report CIS as a separate entity. We reviewed the evidence base for the diagnosis, natural history, treatment, and prognosis of CIS in the lower urinary tract.

2. Evidence acquisition

A systematic literature search was performed in April 2014 using the PubMed, EBSCO, Library of Congress, and Web of Science databases. The search strategy included broad terms in isolation or in combination: *urothelial carcinoma in situ, bacillus Calmette Guerin, intravesical immunotherapy, valrubicin, gemcitabine, hyperthermia, interferon, bladder, prostate, photodynamic diagnosis, fluorescent cystoscopy, narrow-band cystoscopy, natural history, radical cystectomy, lymphadenectomy.* Articles pertaining to upper tract but not lower tract CIS were excluded.

We identified original articles, reviews, and editorials. The following limits were selected: English language, from 1966 to April 2014 (including in press reports), human, and cancer. Guidelines from the European Association of Urology (EAU) and the International Consultation of Urologic Diseases (ICUD) were also evaluated. Abstracts from meetings were excluded from the analysis. Only full-text articles were included.

Manuscripts were reviewed for content relating to diagnostic methods and treatment options for CIS. Many papers pertaining to intravesical therapy included mixed patient populations, and data specific to CIS could not always be extracted. These were included, and this limitation indicated if the results were considered relevant to the treatment of CIS.

Review articles, editorials, commentaries, and letters to the editor were included only if deemed to contain relevant information. Some studies reporting on mixed NMIBC populations were included even if the specific data pertaining to CIS could not be extracted if the content was considered to be important and presumed applicable to CIS. These studies were identified with these limitations in the analysis.

A snowballing technique was used in reference acquisition to identify further relevant studies. Study eligibility was determined by two authors (R.G.C. and P.C.B.) who resolved discrepancies by open discussion.

3. Evidence synthesis

A total of 1887 articles were identified, of which 120 were accepted for evaluation based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis criteria [14] (Fig. 1). Most accepted articles were published between 1995 and 2014.

The focus of the searches was identification of all level 1 scientific papers (systematic reviews and meta-analyses of randomised controlled trials [RCTs]) in accordance with EAU methodology. Panel members (R.G.C. and P.C.B.) rated papers following a classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence [15] (Table 1).

3.1. Classification of carcinoma in situ

CIS is a flat high-grade noninvasive UCC that has a high propensity for invasion and subsequent metastasis. It may occur in any organ lined by urothelium. Cellular anaplasia, loss of polarity, discohesion, nuclear enlargement, hyperchromasia, pleomorphism, and atypical mitoses are the histopathologic hallmarks of CIS. Extensive denudation of the urothelium, monomorphic appearance of the neoplastic cells, inflammatory atypia, radiation-induced nuclear smudging, multinucleation, and pagetoid spread of CIS may cause diagnostic difficulties. Together with clinical and morphologic correlation, immunostaining with CK20, p53 (full thickness), and CD44 (absence of staining) may help accurately diagnose CIS. Urothelial CIS with glandular differentiation or pagetoid changes are variants of CIS that follow the natural history of conventional urothelial CIS [16–18].

Lamm et al proposed a classification of CIS based on clinical parameters [19]:

- Primary: Isolated CIS with no prior/concurrent papillary tumours or CIS
- Secondary: CIS detected at subsequent biopsy with previous non-CIS tumours
- Concurrent: CIS in the presence of any other urothelial tumour

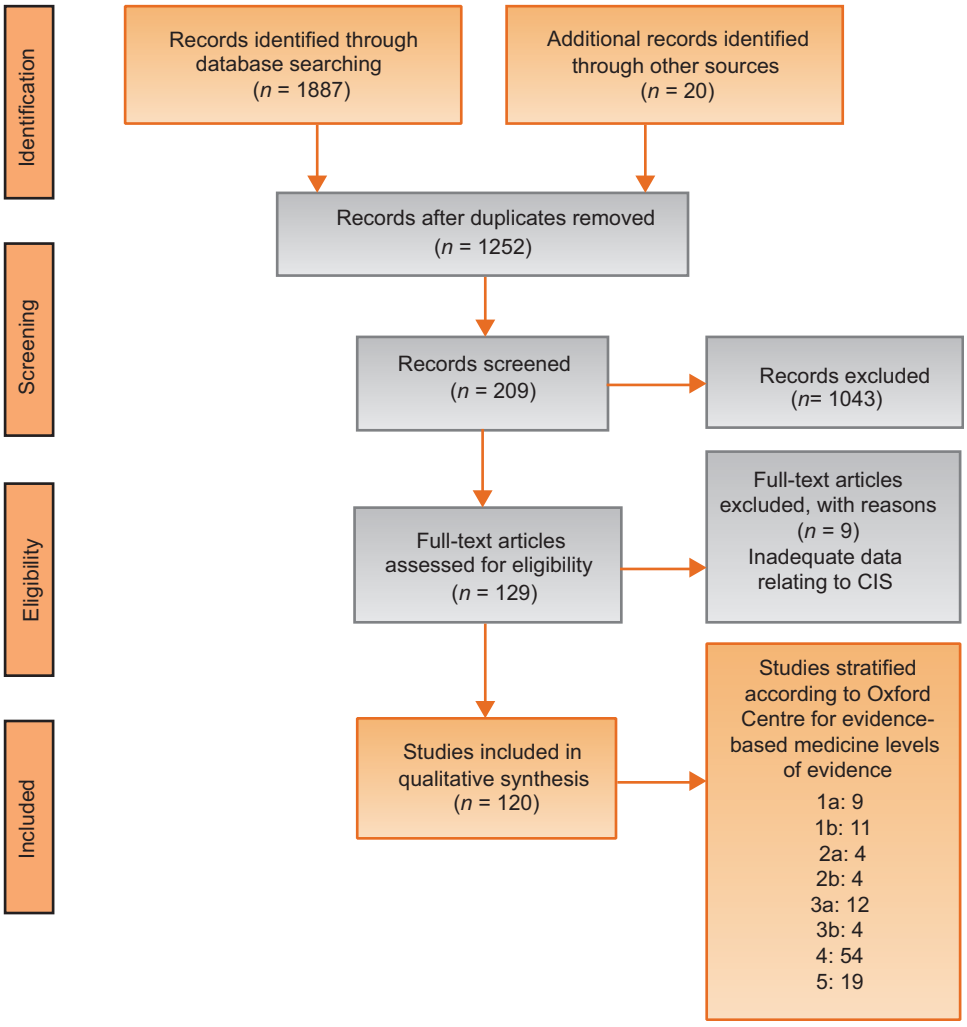

Fig. 1 – Four-phase flow diagram summarising study inclusion based on Preferred Reporting Items for Systematic Reviews and Meta-analysis. CIS = carcinoma in situ.

- Recurrent: Repeat occurrence of CIS after response to intravesical treatment

Primary CIS has been reported in approximately 3% of all patients with bladder cancer (BCa). It is found concurrently with T1 disease in 50% and with muscle-invasive disease (T2–T4) in 60% [20]. Patients with primary CIS have a better response to BCG treatment than those with secondary CIS but have a higher rate of progression and RC. This suggests further work is required to distinguish these entities based on different biologic pathways [21].

The true incidence of CIS remains elusive. Pathologic diagnosis is prone to high interobserver variability (22.7–53.8%) [22–24] with respect to stage and extent of dysplasia [25]. Specialist pathology review should be considered for patients in whom the identification of CIS will alter management [26]. CIS is likely undersampled at the time of bladder tumour resection because it is often not visible, as was revealed by studies with fluorescent cystoscopy. Detection may be increased with urine cytology and random bladder biopsies, although the clinical utility of both in this context is poorly defined [27–29].

CIS is further classified into *focal* (a limited small area of disease either visible or not) or *diffuse* (occurring in two or more biopsies at separate sites), although the clinical implications of this distinction are uncertain. With improved cystoscopic imaging, this classification may become more meaningful in biological terms in the future.

3.2. *Natural history of untreated carcinoma in situ*

Several authors have reported the natural history of CIS in patients treated with resection and/or fulguration alone [30–40] (Table 2). Lamm et al reviewed 14 series and reported progression to muscle-invasive disease in 54% of patients after 4 yr [19], which is consistent with most of the studies listed in Table 2. Cookson et al reported a very similar rate of 53% progression within 15 yr and a 36% rate of RC [33].

Table 1 – Application of Oxford Centre for Evidence-based Medicine Levels of Evidence to the cited references on carcinoma in situ

Level	Evidence type	References
1a	Evidence from meta-analysis of RCT (SR)	[3,4,6,9,10,13,52,56,91]
1b	Evidence from at least one randomised trial	[5,7,32,50,57,61–63,65,77,78]
2a	Evidence from one well-designed controlled study without randomisation	[8,64,71,72]
2b	Evidence from at least one other type of well-designed quasi-experimental study (including low-quality RCT)	[51,54,58,76]
3a	Evidence obtained from well-designed nonexperimental studies such as comparative, correlation, or case studies	[12,24,55,59,67,71,85,86,88–90,100]
3b	Individual case-control study	[72–74,84]
4	Case series (and poor quality cohort and case-control studies)	[21,23,25,26,28,30,31,33–41,53,60,68,69,73–75, 77,79–83,92–94,96–99,101–107,109–120]
5	Evidence from expert committee reports, opinions, or clinical experience of respected authorities	[1,2,11,16–19,22,27,29,42–44,49,66,70,87,95,108]

RCT = randomised controlled trial; SR = systematic review.

The extent of CIS may be relevant for the risk of progression. In the "pre-BCG" studies, it was recognised that extensive CIS was usually symptomatic and much more likely to be associated with tumour invasion [19,33,40,41]. Focal asymptomatic CIS may exist for decades without macroscopic tumour development or invasion [40].

3.3. *Detection of carcinoma in situ*

The detection of CIS was traditionally performed with a combination of urine cytology, cystoscopy, and multiple bladder biopsies [42]. Urine cytology has a sensitivity for any form of CIS of approximately 60% [43]. Within the limitations of random sampling and pathologic assessment, multiple bladder biopsies have a sensitivity of approximately 77% [23]. The most recent ICUD consensus statement [44] recommended urine cytology for all patients at high risk for BCa. Random bladder biopsies, however, are recommended only in specific situations (EAU guidelines). Enhanced cystoscopic techniques have had a considerable impact on the detection of CIS.

Photodynamic detection (PDD) can be particularly helpful in the detection of CIS, with rates of detection increasing from 23% to 68% with WLC alone to 91–97% with WLC plus PDD [4–6]. Kausch et al reported an additional detection rate of 39% for CIS in a meta-analysis of seven studies that specifically reported on CIS [4]. This rate decreased to 23% if the analysis was restricted to five studies with homogeneous patient populations. These cohorts mixed both primary and concomitant CIS. The recurrence rates for all stages were

Table 2 – Natural history of carcinoma in situ treated only with biopsy/fulguration

Study	Subjects, *n*	CIS type	Management	Progression-free survival, mo (range)	Progression rate (%)
Utz et al [30]	62	NA	Fulguration with or without TUR Segmental resection	NA (60–144)	37 (60)
Wolf et al [31]	31 26	Primary Secondary	Cold biopsy with or without TUR	4 (74–129)	16 (52) at 59-mo mean
Herr et al [32]	24	NA	TUR	18 (12–24)	12 (50)
Cookson et al [33]	21	Including Ta/T1	TUR only	6 (3–181)	17 (81)
Jacobsen et al [34]	19	Primary	Surveillance	23 (7–56)	10 (53) at 46-mo mean
Fukui et al [35]	6 1 11	Primary Secondary Concurrent (Ta, T1)	TUR or chemotherapy instillation with or without TUR	30 (6–71) 34 (NA) 16 (8–29)	6 (100) 1 (100) 6 (55)
Melamed et al [36]	17	NA	Fulguration with or without TUR	27 (1–63)	10 (59) at 25-mo mean
Farrow et al [37]	17	NA	Fulguration with or without TUR	40 (7–84)	7 (41)
Althausen et al [38]	12	NA	Fulguration with or without TUR Segmental resection	23 (1–72)	10 (83) at 18-mo mean
Prout et al [39]	12	Primary	TUR	34 (3–60)	9 (75) at 32-mo median
Riddle et al [40]	6	NA	Not specified	49 (6–84)	0

CIS = carcinoma in situ; NA = not available; TUR = transurethral resection.

reduced from 45.4% to 34.5% in favour of PDD, but this difference was largest in the pT1/CIS subgroup. This benefit was also confirmed by Rink et al in a systematic literature review [45]. One meta-analysis contradicted these studies, finding that PDD was not superior to WLC in diagnostic accuracy [10]. It was found to have an advantage in reducing the residual tumour rate but not recurrence or progression rates.

The findings for NBI are more preliminary. In a prospective trial of 220 patients comparing NBI with WLC, 10 additional cases of CIS were found with NBI, and the detection rate improved from 68% to 95% [7]. The clinical impact was not described in this cohort that included mostly T1–T2 UCC. Other authors have reported similar findings [8]. A meta-analysis in 2013 of 1040 patients found NBI increased CIS detection by 28% without an increase in the false-positive rate [9].

The overall impact of better CIS detection is uncertain because it may not alter management of patients who have high-risk NMIBC. The detection of isolated primary or recurrent CIS, or CIS in combination with what would otherwise be intermediate- or low-risk NMIBC should enhance treatment and improve outcomes. This remains to be determined, however.

Another tool for enhanced detection of CIS is the fluorescent in situ hybridisation (FISH) analysis of voided urine to detect amplification of chromosomes 3, 7, and 17 as well as deletion of 9p. Multicolour FISH has been shown to be particularly sensitive and specific for CIS [46]. One series demonstrated that eight of nine patients with a prior history of CIS and a positive multicolour FISH but negative cystoscopy were subsequently diagnosed with a CIS recurrence within 5 mo [47]. This makes FISH potentially valuable in the detection of recurrences on treatment or surveillance. FISH generally outperforms cytology in this context, especially in the setting of intravesical therapy where inflammatory alterations in cytologic features can impair conventional urine cytology [48]. Unfortunately, few studies report on the use of FISH specifically for CIS.

3.4. *Treatment of carcinoma in situ*

3.4.1. *Intravesical therapy*

Intravesical BCG is the generally accepted standard therapy for CIS [49]. Transurethral procedures are generally limited to biopsy, although resection of focal CIS has been described [40,41]. In the era of PDD and NBI, the feasibility of endoscopic control of low-volume focal CIS or even the role of maximal "debulking" of CIS would need to be studied in a controlled fashion, especially in patients who are unsuitable for immunotherapy and/or RC.

The efficacy of BCG specifically for CIS was determined best in the SWOG 8507 trial comparing induction therapy only with induction plus maintenance in a prospective and randomised fashion [50]. The complete response (CR) rate at 3 mo (after induction therapy) was 57% and 55% in the induction-only and the maintenance arms of the trial, respectively. The CR rate after 6 mo increased to 68% in the induction-only arm and to 84% in the maintenance arm (after the first course of maintenance; $p = 0.004$). This trial demonstrated not only the benefit of maintenance BCG but also the potential delayed benefit of BCG in the treatment of CIS and the necessity to wait for 6 mo before assessing response to treatment with a repeat bladder biopsy. A potential error in clinical practice is to determine that a patient has failed BCG at 3 mo and move to alternative strategies prematurely [51]. Unfortunately, the longer term outcomes of patients with CIS in SWOG 8507 are not reported separately, and there is a paucity of long-term data after maintenance therapy [52].

Chade et al [53] described outcomes in a cohort of 155 patients with primary CIS managed with induction BCG only. There was no evidence of disease at 6 mo in 62% of patients. The 5-yr cumulative incidence of progression to cT1 or higher was 45% and progression to cT2 or higher was 17%, adjusting for the competing risk of RC. BCG responders were significantly less likely to progress. Despite BCG therapy and early RC, patients with primary CIS had high rates of progression.

The same group, in a second study comparing primary and secondary CIS [21], determined that primary CIS was associated with a higher risk of progression than secondary CIS even though the response rate at 6 mo was higher. This series and others [54,55] clearly demonstrate the high-risk biology of primary CIS, although further benefit may have been achieved with maintenance BCG.

A nihilistic view in the treatment of CIS suggests that BCG simply defers the inevitable need for RC. Although the early disease-free rates of BCG therapy are high, the treated natural history does reflect high rates of recurrence and progression. In one phase 2 trial, 50% of patients with CIS receiving intravesical BCG (no maintenance) were alive with retained bladders after 7.6 yr of follow-up, although 60% had experienced a recurrence. Another 7 patients underwent RC and were still alive; 16 (20%) died due to BCa. Two patients underwent RC for severe cystitis with bladder contraction [54]. Because the alternative is immediate RC, these results may be acceptable to most patients.

BCG has been compared with intravesical chemotherapy mostly in studies that do not delineate CIS from other stages of NMIBC [56] (Table 3). In a European Organisation for Research and Treatment of Cancer (EORTC) phase 3 trial, BCG was compared with epirubicin specifically in 168 patients with primary (23%), secondary (24%), and concurrent CIS (52%) [57]. Maintenance therapy was administered in both treatment arms. The 3-mo CR rates for BCG and epirubicin were similar, but the time to recurrence in patients who achieved a CR was reduced after epirubicin (median: 1.4 vs 5.1 yr), and CIS recurrences were more frequently observed (45% vs 16%).

The optimal duration of BCG maintenance is often debated because the 3-yr period was determined arbitrarily and the toxicities of prolonged therapy are significant. However, BCG is the primary treatment for CIS (and not just adjuvant therapy after tumour resection as for other stages), so one could speculate that longer maintenance would be most important. A recent EORTC trial compared 1 yr with 3 yr, and a one-third dose to full dose excluded patients

Table 3 – Intravesical therapy for carcinoma in situ

Study	Therapy	Subjects, *n*	Follow-up, mo	CR (%)	Rec (%)	5-yr Prog (%)	RC (%)	Comments
Lamm et al [50]; SWOG 85–07	BCG induction with vs without maintenance (CIS subgroup reported)	278	~90	84 68		–	–	Other outcomes only reported for mixed NMIBC cohort
Chade et al [53]	BCG induction only (CIS only)	155	40–49	62	–	45	–	High rates of progression with primary CIS
Chade et al [21]	BCG induction only Primary CIS Secondary CIS	 221 255	61	 65 39	 82 73	 43 32	 42 32	Higher rates of progression to cT1 or cT2 in primary CIS
Jakse et al [54]; EORTC 30861	BCG induction only (primary CIS)	103	91	75	60	–	9	20% dead of bladder cancer; high rate of local toxicity
Griffiths et al [55]	BCG induction only Primary CIS CIS and Ta CIS and T1	135	41	 74 70 75	– 	 20 18 49	 40 42 70	Poor results for CIS and T1 disease with induction only
de Reijke et al [57]	epirubicin vs BCG with maintenance (primary/secondary/ concurrent CIS)	168	67	56 65 (ns)	45 16	60 40	30 23	Time to recurrence longer with BCG (1.4 vs 5.1 yr)
Witjes et al [60]	MMC and hyperthermia 17 BCG naive 34 BCG failures (primary/secondary CIS)	51	27	92	49 at 2 yr	–	5	No difference between groups
Di Stasi et al [61]	EMDA MMC vs MMC vs BCG (mainly patients with CIS and concurrent T1)	108	43	58 31 64	47 25 47 at 4 yr	17 22 17 (ns)	5 7 8 (ns)	Crossover allowed; intention-to-treat analysis
Di Stasi et al [62]	BCG and EMDA MCC vs BCG (mixed high-risk NMIBC)	212	88	52 71	48 71	17 61	–	57 patients with CIS only
Rosevear et al [72]	BCG and interferon-α BCG naive BCG failure (primary/secondary/ concurrent CIS)	 111 120	25	 76 66	 40 43–77 at 2 yr	–	–	63% pure CIS
Dinney et al [77]	Valrubicin (CIS post BCG failure/intolerance)	80	–	18	–	–	25	Analysis of phase 2/3 and phase 3 trial in BCG-refractory CIS
Gontero et al [80]	Gemcitabine (BCG naive) (primary, secondary, concurrent CIS)	18	5	44	–	–	–	Phase 2 trial aborted due to side effects
Skinner et al [81]; SWOG S0353	Gemcitabine (BCG failure)	47	24	21	85	4	36	Mixed NMIBC, 60% CIS
Barlow et al [82]	Docetaxel (BCG failure)	54	39	59	25		24	Mixed NMIBC, 60% CIS Single-centre phase 2
Morales et al [83]	Mycobacterial cell wall-DNA complex (BCG naive and failure) (primary, secondary, concurrent CIS)	55	26	46 (8-mg dose)	–	–	–	Multicentre, open-label of two doses (4 mg in *n* = 25 and 8 mg in *n* = 30)

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; CR = complete response; EMDA = electromotive drug administration; EORTC = European Organisation for Research and Treatment of Cancer; MMC = mitomycin C; NED = no evidence of disease; ns = not specified; NMIBC = non–muscle-invasive bladder cancer; Prog = progression; RC = radical cystectomy; Rec = recurrence; RFS = recurrence-free survival.

with CIS [58]. Patients in the high-risk group, to which we would usually attribute CIS, benefitted most from 3 yr of full-dose therapy. Three years of maintenance therapy remain the standard.

Device-assisted therapy including intravesical hyperthermia with mitomycin C (MMC) instillation [59,60] and electromotive drug administration (EMDA) of MMC [61] are newer advances that enhance MMC delivery and efficacy. Both have been shown to be efficacious in high-risk NMIBC but not specifically for CIS. One could speculate that enhanced tissue penetration is less relevant in the context of CIS. However, Witjes et al [60] demonstrated the safety and efficacy of intravesical MMC with hyperthermia in a multicentre trial of 51 patients with CIS (17 BCG naive and 34 BCG failures). A CR was observed in 45 of 49 evaluable patients, and 50% had a durable response at 2 yr. Both technologies appear to be reasonable options in patients who cannot tolerate BCG therapy. EMDA MMC appears

most efficacious when alternated with BCG [62]. Of note, other attempts to alternate MMC without EMDA and BCG have not proven advantageous over BCG alone [63–65].

3.4.2. Second-line therapy

Standard therapy for BCG-refractory CIS of the bladder is RC [66]. In patients who are unsuitable for or refuse RC, second-line intravesical salvage therapy can be considered, but little evidence supports such interventions. For all patients experiencing a recurrence of CIS after prior intravesical BCG therapy, it is important to consider the upper tracts and the prostatic urethra as possible sites of recurrence before proceeding with further interventions [67,68].

An additional course of BCG with or without interferon-α (INF-α) is an option for patients with CIS failing BCG therapy. There is evidence that a repeat challenge for relapsing CIS after a disease-free interval >12 mo is likely to respond a second time [69]. For BCG-refractory disease or relapses within <12 mo, the CR rate is <50% and only rarely durable [69]. Each subsequent course of BCG increases the risk of progression [70].

A relative paucity of data supports the use of BCG plus INF-α. The combination was used in a large phase 2 trial in both BCG-naive patients and those who had failed previous BCG therapy [71]. Of the 1007 evaluable patients, 59% of BCG-naive and 45% of BCG-failure patients remained disease free at a 24-mo median follow-up. In both cases, however, there was no clear advantage over BCG monotherapy. Results for CIS were not discernible from the overall results. In another phase 2 trial [72], factors determined to affect response to BCG plus INF-α for CIS were prior tumour stage and two or more BCG failures.

A number of studies have examined the benefit of a second course of BCG. Bui and Schellhammer [73] examined administration of a second course to those recurring after CR to the first course. Overall, 82% achieved a second CR, and 43% remained tumour free at a median follow-up of 87 mo. Bretton et al [74] in their study determined that in those who required a further course, success was more likely in those who had a prolonged response to the initial treatment. However, disease progression occurred in 46% of those who required a further course. Finally, Lockyer et al [75] showed that patients with BCG failure on the initial surveillance cystoscopy had a poor prognosis with 60% progression and 40% death from urothelial carcinoma (UC).

Intravesical valrubicin is the only salvage agent approved by the Food and Drug Administration, although it was approved with a minimal amount of evidence to support its clinical utility. In the valrubicin study, the drug was administered via six weekly instillations to patients with recurrent CIS after BCG. Of 90 patients, 21% were disease free at 9 mo; only 8% were disease free at 30 mo [76]. In a further study of BCG failure and intolerant patients, the CR rate was 18% at 3 mo and 4% at 2 yr [77]. The benefit is marginal and does not warrant delaying RC in patients who can tolerate cystectomy, but it does offer an option in cases where RC is not possible.

Intravesical gemcitabine has demonstrated activity in BCG-refractory NMIBC [78], and one phase 2 trial was completed specifically in patients with treatment-naive CIS [79]. This latter study revealed excessive toxicity and reduced activity [80]. In the SWOG S0353 phase 2 study, 20 of 47 patients had pure CIS and had failed two prior courses of BCG. A CR was observed in 47% at 3 mo, 28% at 1 yr, and 21% at 2 yr with maintenance therapy [81].

In all of these studies, and others with intravesical docetaxel [82] and mycobacterial cell wall DNA complex [83], the treatment arms were small and heterogeneous. Further studies are required in the CIS setting for both BCG-naive and BCG-refractory disease to determine the optimal treatment schedule and benefit of maintenance therapy.

No validated and reliable biomarkers are currently available to predict response to intravesical BCG. A number of studies have examined urine cytokines following treatment as a surrogate for response [84–87], and others have focused on tissue markers such as p53 and Ki-67 [88]. More recently, Nunez-Nateras et al [89] examined the balance between T helper (Th)1 and Th2 signatures in the tumour microenvironment prior to BCG. They determined that if a tumour exists in a Th2 environment and has yet to be exposed to a Th1 inflammatory response, then BCG therapy, which would be expected to incite a Th1 response, should be beneficial. Further prospective studies will need to be carried out to validate the usefulness of this immunohistochemical metric.

3.4.3. Immediate versus delayed radical cystectomy for carcinoma in situ

Many patients with treatment-naive primary CIS are treated with intravesical BCG, and RC is withheld until recurrence. Immediate RC, however, is a rational alternative. There have been no clinical trials comparing immediate RC with bladder preservation with intravesical BCG therapy. Most studies have a negative selection bias against delayed RC because only patients progressing during or after conservative treatment are treated radically.

As with all high-risk NMIBC, a balance must be struck between overtreatment with RC and undertreatment with subsequent disease progression when administering BCG [2,75,90]. It has not been demonstrated that an initial trial of BCG immunotherapy, followed by salvage RC for patients who fail to achieve a CR or who recur, affects overall survival compared with immediate RC [91–93]. However, progression to invasive disease likely occurs in a delayed fashion in patients with CIS. Cookson et al reported that 53% of BCG-treated patients experienced disease progression within 15 yr, and 36% eventually underwent RC for progression or refractory/recurrent CIS [33]. The same group reported that patients with NMIBC who have RC within 2 yr of BCG treatment do better than those with RC later [94]. Long-term follow-up is therefore necessary to draw conclusions about treatment options for CIS.

Early RC can be justified not only by the risk of progression, but also by the risk of understaging [95]. Several series indicate that up to 53% of patients with primary CIS may be understaged at RC either due to incomplete restaging transurethral resection, upper tract disease, or prostatic stromal disease [96–98]. Most series find approximately 20%

Table 4 – Outcomes after cystectomy for carcinoma in situ of the bladder

	Study	Clinical stage	Pathologic stage	Subjects, *n*	Follow-up, mo	LNs removed	pN1–3 (%)	≥pT1 (%)	RFS	OS	Recurrence location
Clinical Tis	Tilki et al [96]	Tis	48% Tis 8% T0 8% Ta 13% T1 23% T2–T4	243	37.3	25	14 (5.8)	87 (36)	5 yr 74%	5 yr 85% CSS	NA
	Cheng et al [93]	Tis	NA	138*	132	NA	1	NA	5 yr 90% 10 yr 82% CSS	5 yr 75% 10 yr 58%	1 local 20 distant
	Stein et al [100]	Tis	NA	100	122	NA	5+	NA	5 yr 91% 10 yr 89%	5 yr 89% 10 yr 72%	NA
	Huang et al [98]	Tis		27	94	29	1	9 (33)	5 yr 100% 10 yr 83%	5 yr 87% 10 yr 56%	1 upper tract 1 urethra
	Amling et al [102]	Tis	35% Tis 35% T0 22% T1 9% T3	23					5 yr 100% 10 yr 92%		NA
Pathologic Tis	Shariat et al [97]	48% Tis 6% Ta 23% T1 23% T2	Tis	99	39.2	18	3	46 (48)	5 yr 83% 10 yr 83%	-	5 local 5 distant 1 both
	Zehnder et al [99]	Tis	Tis	52	102	36	0	0	5yr 94% 10 yr 90%	5 yr 85% 10 yr 66%	1 local 1 distant 2 upper tract
	Hassan et al [92]	38% Tis 2% Ta 16% T1 44% T2	Tis	50	37.2	29	2	NA	3 yr 88%		2 local 4 distant

CSS = cancer-specific survival; LN = lymph node; NA = not available; OS = overall survival; RFS = recurrence-free survival.
* Only 75 underwent radical cystectomy.

of patients with pT2 disease or higher in the final specimen. In one series, this understaging rate was 14.3% in patients who underwent immediate RC versus 36.8% in those who previously failed BCG [98].

Table 4 summarises the outcomes after RC for CIS. The series from Zehnder et al is remarkable because it includes only patients with both clinical and pathologic CIS, and it excludes patients with concomitant more invasive disease [99]. This series demonstrated a 90% 10-yr recurrence-free survival (RFS). In the largest series reported to date, Tilki et al [96] described a multicentre international cohort of 243 patients who underwent RC for primary CIS who had failed bladder-conserving therapy. This cohort represented 7.6% of 3207 patients in a larger RC cohort. The authors noted the same pathologic stage (pTis) in 48%, downstaging (pT0 or pTa) in 16%, and upstaging in 36% including 13% pT1, 12% pT2, 5% pT3, and 6% pT4. Lymphovascular invasion was found in 9% of specimens, and 6% had nodal metastasis consistent with other series [92,98,100]. The survival rates are indicated in Table 4. These authors highlight the need for further research to identify the higher risk patients with aggressive disease. Clearly vigilance is required in the management and surveillance of patients with CIS to prevent adverse outcomes.

The risk of understaging has direct implications for the extent of pelvic lymph node dissection performed in patients with primary CIS. The rates of upstaging and pelvic lymph node involvement reported by Tilki et al would suggest that a pelvic node dissection is necessary, but little evidence is available to guide how extensive this dissection should be. In a prospective lymph node mapping study of 114 patients with cTa/Tis/T1 BCa who underwent RC and concomitant "superextended" lymph node dissection up to the inferior mesenteric artery, nine patients (8%) had lymph node metastases [101]. Twenty-five patients in the cohort had cTis only, of whom 20% were upstaged to pT2 or higher at RC and three had nodal metastases (3 of 25, 12%). Three patients had involved lymph nodes at level 3, of whom all three also had level 1 and 2 nodal metastases. One of these patients had cTis disease. The evidence is inadequate to make treatment recommendations.

In large RC series, pTis only is found in 3–9% of patients (Table 5) [96,100,102–107]. Most series do not indicate in what proportion of cases the indication for surgery was made based on a diagnosis of clinical CIS only. Shariat et al [97] specifically analysed 99 patients with pTis only and found the preoperative staging to be cTis only in 47%, cTa in 7%, cT1 in 23%, and cT2 in 23% (all with or without concomitant CIS). The outcomes in these patients were excellent with RFS estimates of 83.0% at 5 and 7 yr after RC and disease-specific survival estimates of 90.7% at 5 yr and 87.2% at 7 yr. Six patients (6%) died of BCa. Similar results were noted in the University of Southern California RC series [100] with 5- and 10-yr RFS rates of 91% and 89% for pTisN0 disease. Although these results are favourable, they did not differ from patients

Table 5 – Rates of clinical and pathologic stages in large cystectomy series

	Study	Subjects, *N*	cTis *n* (%)	pTis *n* (%)
Tis only	Amling et al [102]	531	23 (4.3)	19 (3.6)
	Stein et al [100]	1054	–	100 (9)
	Shariat et al [105]	888	83 (9.3)	52 (5.6)
	Tilki et al [96]	3270	243 (7.4)	117 (3.6)
	Yafi et al [107]	2287	78 (3.4)	150 (6.6)
Mixed pT0/Ta/Tis	Madersbacher et al [103]	507	–	17 (3.4) pTa/Tis
	Hautmann et al [104]	788	–	43 (5.5) pTa/Tis
	Ghoneim et al [106]	2720	–	286 (10.5) pT0/Ta/Tis

with pT2N0 disease who had 5- and 10-yr RFS rates of 89% and 87%. However, cT2 BCa is associated with a better outcome when it is downstaged to pTis than when it remains muscle invasive at RC [92,108].

3.5. *Prostatic carcinoma in situ*

3.5.1. *Prevalence and detection*

The incidence of primary de novo prostatic CIS is very low. Approximately 90% of CIS of the prostatic CIS is found in association with a papillary or invasive UC, which is typically located in the bladder [109]. The risk is increased in the presence of CIS of the bladder or multifocal bladder tumours, especially when involving the bladder neck [110–113]. Up to 40% of patients followed after treatment for high-grade NMIBC may develop metachronous recurrence in the prostatic urethra and ducts at 15 yr, usually in conjunction with relapse in the bladder [109].

It is critical to determine the extent of prostatic CIS accurately. Biopsy of the prostatic urethra is ideally performed with the resectoscope and a loop electrode at the 5 and 7 o'clock positions from the bladder neck to the level of the verumontanum to include the ejaculatory ducts [114]. This allows for detection of penetration into the prostatic ducts (pdCIS) or the prostatic stroma (psCIS). Twenty percent of cases are limited to the prostatic urethra (puCIS); 47% are pdCIS and approximately 33% are combined. Of those cases that invade the prostatic stroma, 26% represent direct penetration from a primary bladder tumour and 74% arise from puCIS and pdCIS [115]. Tangential sectioning of CIS in the prostatic ducts can be misinterpreted as stromal invasion, which can lead to overtreatment.

Most of the information about CIS of the prostate has been reported in RC specimens, and little information is available about prostatic involvement in patients treated with bladder preservation. Most studies report prostatic involvement by all stages of carcinoma and not specifically CIS. Liedberg and colleagues performed two mapping studies of the bladder and prostatic urethra in patients planned for RC and compared the transurethral biopsy findings with the RC findings. In the first study [113], 29% (50 of 175) of cystoprostatectomy specimens contained UC in the prostatic urethra and/or prostate. Preoperative resectional biopsies of the prostatic urethra in 154 of these patients identified 31 of 47 cases (66%) with UC in the prostatic urethra/prostate, with a specificity of 89%. The detection of stromal invasion and nonstromal involvement was similar: 66% and 65%, respectively. Very similar results were found with respect to CIS, specifically in the second report from this group [116]. Resection biopsies of the prostatic urethra in 162 men undergoing cystoprostatectomy demonstrated a sensitivity of 51% and specificity of 83% for CIS only. The authors concluded that negative findings should be considered unreliable.

By definition, psCIS is by definition no longer CIS and requires aggressive treatment. Wishnow and Ro [117] selected 23 patients in their cystectomy series who had multifocal pTis in the bladder associated with CIS of the prostatic ducts. In five of these patients the tumour invaded the prostatic stroma (invasive UC of prostatic ducts), and all five of these patients had metastases.

3.5.2. *Management*

There is little evidence regarding pdCIS in the literature, so treatment recommendations vary from biopsy followed by intravesical BCG to cystoprostatectomy, especially in deeper ductal/acinar involvement. Particularly with pdCIS, there is a risk of understaging, as highlighted by the Wishnow and Ro series [117].

Palou et al reported specifically on UC of the prostate as a chapter in an ICUD statement on BCa [109]. They advocated treating prostatic CIS with intravesical BCG and compiled data from several small series indicating a response of 70% in the prostatic urethra itself and a combined response in the bladder and prostate of 42–72%. Others cite the common finding of BCG granulomatous lesions in the prostate as a sign that BCG has penetrated into the prostate where it is presumed to have a similar effect as in the bladder [118].

Gofrit et al [119] compared pooled CR rates of small studies not using transurethral resection of the prostate (TURP) with those of studies using TURP before immunotherapy, and they found a significantly higher prostatic urethra CR rate for the TURP group (95% vs 66%). The presumption is that TURP may increase accurate staging, remove the maximal amount of affected tissue, and perhaps permit better BCG penetration.

Herr et al suggested that extensive intraductal CIS is likely best managed with radical surgery over conservative management [120]. These authors analysed a cohort of 186 patients with NMIBC who had a minimum follow-up of 15 yr. Relapse in the prostate was observed in 72 (39%). Most of these (61%) had a relapse in the first 5 yr, but another 39% had a relapse after 5 and up to 15 yr. A total of 50 patients (69%) were alive at last follow-up; 22 (31%) died of UC. Stromal invasion was associated with extravesical tumour invasion in almost half of the cases, and intraurethral stromal invasion was most often associated with in situ or minimally invasive tumour confined to the bladder.

3.6. Limitations of the systematic review

This study represents a comprehensive literature review of a clinically relevant topic that has not previously been reviewed in this form. A major limitation of this work, as highlighted throughout the text, is the relatively poor quality of the primary data and the paucity of prospective RCTs in this domain. Almost all studies were retrospective single-institution reports with poorly standardised methodology. In many studies specific data pertinent to CIS cannot be extracted from the mixed populations of patients with NMIBC. However, all findings were endorsed by the authors of this paper, who make up a panel of international experts on this topic. The findings highlight the need for more formal study of CIS of the lower urinary tract in clinical trials.

4. Conclusions

Urothelial CIS is a distinct entity with a spectrum of biologic potential. The most significant advancement in the past 2 decades has been the advent of new imaging technologies that have markedly enhanced detection of CIS in the bladder. Intravesical BCG remains an efficacious therapy, but failure rates are high, and only a few incremental advances have been made in the management of bladder CIS. Prostatic CIS is a particular clinical challenge due to the risk of occult invasive disease that has a high propensity for progression. Although organ preservation may be indicated for CIS of the bladder and prostate, vigilance is required, and RC should be considered for BCG-refractory disease, BCG intolerance, and extensive intraductal CIS of the prostate. There is a clear clinical unmet need for improved localised therapies including novel intravesical agents to enable more frequent bladder preservation without increasing the risk of progression.

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Study concept and design: Casey, Shariat, Catto, Black.
Acquisition of data: Casey, Black.
Analysis and interpretation of data: Black, Casey.
Drafting of the manuscript: Casey, Black.
Critical revision of the manuscript for important intellectual content: Casey, Catto, Cheng, Cookson, Herr, Shariat, Witjes, Black.
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